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ETABOLISM OF NOREPINEPHRINE IN RAT
TISSUE HOMOGENATES, 2 NA 8 4
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Aerospace Medical Division (AFSC)
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FOREWORD

This report was prepared by the following personnel in the Biokinetics Branch:

⑩ by JOSEPH L. BOROWITZ, ^{and} ~~Ph.D.~~
JAMES H. MERRITT, ~~B.S.~~

The technical advice and assistance of William Lackey is acknowledged.

ABSTRACT

→ In this study, tissue homogenates served as convenient systems in which to investigate the metabolism of norepinephrine. Iproniazid was found to delay the disappearance of norepinephrine from rat brain homogenate. The effect became significant after 4 hours of incubation. High concentrations of magnesium (1.2×10^{-2} M) counteracted this effect of iproniazid. Large doses of magnesium, however, did not affect the increased brain norepinephrine level produced by iproniazid in rats. Oxalate, 3.2×10^{-2} M, did not inhibit the decay of norepinephrine in rat brain homogenates, but in one experiment it enhanced the effect of iproniazid in this system. In a limited number of experiments, both iproniazid and oxalate delayed the disappearance of norepinephrine from rat heart homogenate. ↖

X - 1.2 lines 1.2 h. - 2 M
XX - 3.2 lines 1.2 h. - 2 M.

This technical documentary report has been reviewed and is approved.

Robert B. Payne
ROBERT B. PAYNE
Colonel, USAF, MSC
Chief, Operations Division

METABOLISM OF NOREPINEPHRINE IN RAT TISSUE HOMOGENATES

1. INTRODUCTION

Because it is difficult to study the metabolism of norepinephrine in individual organs using whole animals, our knowledge of the metabolism of this substance in any given tissue is not complete. Studies involving isolation and quantitation of metabolites of injected radioactive norepinephrine are not definitive since the metabolites isolated from a particular tissue may have been formed elsewhere, at least in part. Analyses of urinary metabolic products also reflect processes which occur in many different tissues.

To understand the mechanism of action of drugs of the monoamine oxidase inhibitor type, as well as the function of norepinephrine (e.g., in brain), it is important to know how norepinephrine is metabolized in individual tissues.

To insure participation of only one tissue in the metabolism of norepinephrine in this study, homogenates of rat brain and heart were used. The effect of various substances on the disappearance of endogenous norepinephrine from these homogenates was determined.

2. MATERIALS AND METHODS

Homogenization and incubation

Brains or hearts from 5 to 8 male albino rats weighing 350 to 500 gm. were pooled and homogenized by use of glass tissue homogenizers. One gm. of tissue was suspended in a total of 6 ml. of homogenate. Phosphate buffer, pH 7.4, 0.1 M, was used as the media. This procedure required 20 to 30 minutes.

Much of this work was presented before the Federation of American Societies for Experimental Biology, Atlantic City, N. J., April 1961.

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The homogenates in 250 ml. beakers were then incubated in a Dubnoff metabolic shaker at 37° C. The preparations were shaken slowly in air. Aliquots of 6 ml. were removed at hourly intervals and analyzed for norepinephrine.

Estimation of norepinephrine

The method of Shore and Olin (1) was used with certain modifications. For ease of handling, 1 gm. of tissue was suspended in 6 ml. of homogenate rather than in 2 ml. as suggested by Shore and Olin. The final extraction was into 8 ml. rather than 5 ml. of 0.01 N HCl. Two aliquots (3 ml. each) of this final extract were used for each determination, one serving as the blank. The iodine and thio-sulfate solutions were mixed before being added to the blank. The number of fluorescent units equivalent to 1 gamma of norepinephrine was determined by addition of 1 gamma of authentic norepinephrine to a duplicate sample before extraction. The increment in fluorescence thus produced was taken to be equivalent to the norepinephrine added, and amounts of norepinephrine in the samples were calculated from this information.

Because the values for norepinephrine in rat heart and brain obtained in this study by the method of Shore and Olin were greater than those reported by others using various methods, the results were checked by using the procedure followed by Trendelenburg and Weiner (2). This procedure, which was carried out at room temperature, is specific for norepinephrine and epinephrine and excludes closely related compounds such as dopamine and normetanephrine.

The latter method was used, also, to trace the disappearance of norepinephrine in nor-

mal and iproniazid-treated rat brain homogenate. The values obtained were in line with those reported in the literature. Although these results differed quantitatively from those obtained by the method of Shore and Olin, qualitatively they were in good agreement, allowing for the fact that the method of Shore and Olin does not entirely exclude dopamine or normetanephrine (3, 4, 5). So, except for a small percent of fluorescence due to dopamine, normetanephrine, and perhaps epinephrine, the values reflect the norepinephrine present and are represented accordingly. The results of this study therefore provide an estimate of the relative effects of various substances on breakdown of norepinephrine in rat tissue homogenates.

Drugs

Iproniazid, 100 mg./kg., as the phosphate salt, was injected intraperitoneally 12 to 24 hours prior to sacrificing. Also, in two experiments iproniazid was added to brain homogenate from untreated rats at the beginning of incubation to make a concentration of 10^{-3} M. Oxalate was added to the homogenates to make a concentration of 1.3×10^{-2} M, 3/5 by weight as the ammonium salt and 2/5 as the potassium salt. S-adenosylmethionine was also added to brain homogenate not only initially but also at hourly intervals thereafter in the amount 1 μ M. per gram of tissue. Two hundred μ M. of $\text{MgCl}_2 \cdot 6 \text{H}_2\text{O}$, per gram of tissue was added at the beginning of incubation. The quantity of magnesium used is analogous to that used by Axelrod (6) in his study of the isolated catechol-O-methyltransferase system.

3. RESULTS

Brain homogenates from rats pretreated with iproniazid do not metabolize endogenous norepinephrine as rapidly as controls except perhaps for the initial period of incubation (fig. 1). This effect is not related to the difference between control and iproniazid-treated rats in initial levels of brain norepinephrine, for two reasons: (1) Addition of iproniazid (10^{-3} M) to brain homogenate from untreated rats produced the same results as pretreatment of

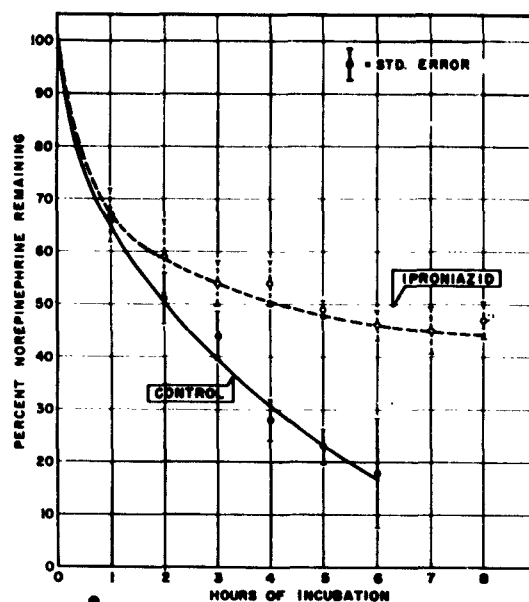


FIGURE 1

Disappearance of norepinephrine from rat brain homogenate. The percent norepinephrine remaining is significantly different at 4, 5, and 6 hours. Initial values: control, 0.83 gamma/gram \pm 0.10 standard error; iproniazid, 2.01 gamma/gram \pm 0.17 standard error.

the animals with iproniazid. When hours of incubation were plotted against percent norepinephrine remaining, a curve identical to the one shown for iproniazid in figure 1 was obtained in two experiments in which iproniazid was added to untreated brain homogenate. (2) Addition of norepinephrine to normal brain homogenate to make the initial level correspond to that in homogenates from iproniazid-treated rats did not change the disappearance curve shown for control in figure 1. It seems therefore that the percent of norepinephrine which disappears from rat brain homogenates after a given period of incubation is independent of the initial concentration of norepinephrine. This, of course, is not necessarily true beyond the concentrations tested, but seems to hold both in the presence and in the absence of iproniazid in the experiments performed.

When rat brain homogenate was brought to a temperature of 70° C., and maintained at

that temperature for 5 minutes, the subsequent disappearance of norepinephrine was markedly slowed. Seventy-eight percent of the original fluorescence remained after 4 hours of incubation as opposed to 28 percent in unheated brain homogenates. When rat heart homogenate was heated up to 96° C. prior to incubation, approximately 60 percent of the original fluorescence remained after 4 hours of incubation. This was taken as evidence for the enzymatic dependence of most of the disappearance process in both tissues.

The amount of norepinephrine remaining at hourly intervals through 7 hours was not significantly changed by addition of oxalate to brain homogenate in three experiments. In one experiment, oxalate was added to brain homogenate from iproniazid-treated rats and the disappearance of norepinephrine traced through 7 hours. This curve resembled that obtained with heated brain homogenate which was carried through 4 hours.

Two experiments were done in which the disappearance of norepinephrine was followed in brain and heart homogenates from rats treated with 500 mg./kg. of pyrogallol intraperitoneally 30 minutes prior to sacrificing. The rate of decay of norepinephrine was decreased by pyrogallol in both brain and heart homogenate. However, an effect by pyrogallol (10^{-3} M) was also noted in heated brain homogenate. Pyrogallol reduced the rate of decay in this system to about the same extent as in unheated homogenate. Since enzymes were presumably inactive in the heated homogenate, the effect of pyrogallol was thought to be primarily nonenzymatic, and probably related to the antioxidant property of this substance.

In the presence of iproniazid, the methylating system was assumed to be very active in metabolizing norepinephrine. Exhaustion of CH_3 donor from the system seemed a likely explanation of the effect of iproniazid. When the cofactors S-adenosylmethionine, a methyl donor, and magnesium, also known to be necessary for proper function of the methylating

system, were added to iproniazid-treated rat brain homogenate, the decay of norepinephrine was nearly the same as that in controls. It was later found, however, that the magnesium in the high concentration used was primarily responsible for antagonizing the effect of iproniazid. Magnesium alone reduced the percent of norepinephrine remaining at 4 hours from 54 to 26 percent in iproniazid-treated brain homogenate ($P < .01$). Addition of S-adenosylmethionine alone to iproniazid-treated brain homogenate had only a slight effect on the percent of norepinephrine remaining since at the end of 5 hours of incubation 39 percent of the initial catecholamine fluorescence was still present.

The effect of magnesium in the homogenate system prompted an attempt to use magnesium to antagonize the effect of iproniazid in vivo. Mice were given 200 mg./kg. intraperitoneally of iproniazid and 4 hours later half of them were given 500 mg./kg. of $\text{MgCl}_2 \cdot 6 \text{H}_2\text{O}$ intraperitoneally in two doses. Fifteen minutes later, all mice received 200 mg./kg. of L-dihydroxyphenylalanine (DOPA) also intraperitoneally. The magnesium-treated group was noted to be much less active and aggressive than the control group subsequent to the administration of DOPA. It seemed that the magnesium had canceled the influence of iproniazid pretreatment on the effects of DOPA.

Magnesium's antagonism of iproniazid in brain homogenate and in vivo in mice indicated that large doses of magnesium might cancel the increase in brain norepinephrine known to be produced by iproniazid. Accordingly, 20 rats were given iproniazid 100 mg./kg. and 16 hours later, 10 were treated with magnesium. (Five rats received three doses of 150 mg./kg. $\text{MgCl}_2 \cdot 6 \text{H}_2\text{O}$ intraperitoneally over a period of 1 hour and the other 5 received two doses of 100 mg./kg. intraperitoneally at an interval of $\frac{1}{2}$ hour.) Thirty minutes later, the animals were sacrificed by cervical dislocation and their brains removed. The brain norepinephrine content was estimated by the method used by Trendelenburg and Weiner and found to be 0.71 ± 0.06 gamma/gram (\pm standard error)

in the magnesium-treated group and 0.68 ± 0.06 gamma/gram in controls. Therefore, under the conditions of these experiments, magnesium does not alter the increased levels of norepinephrine produced by iproniazid.

Norepinephrine disappears more rapidly from rat heart than rat brain homogenate but this is also true when the homogenates are heated. Iproniazid delays the metabolism of norepinephrine in rat heart homogenate (fig. 2), and despite the limited number of

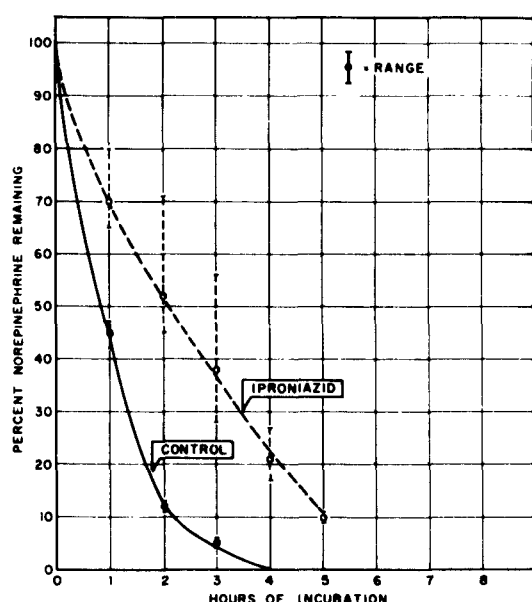


FIGURE 2

Disappearance of norepinephrine from rat heart homogenate. Initial values: control, 1.45 gamma/gram ± 0.11 standard error; iproniazid, 1.64 gamma/gram ± 0.31 standard error.

experiments accomplished, the percent of norepinephrine remaining at 1 and 2 hours is significantly different in the control as compared to iproniazid-treated heart. Oxalate, which had no effect in brain, decreased the disappearance of norepinephrine from rat heart homogenate to a degree similar to iproniazid in three experiments.

4. DISCUSSION

Iproniazid's ability to prolong the life of norepinephrine in rat brain and heart homogenate is very likely related to the ability of this substance to increase the levels of norepinephrine in these tissues in vivo (7). The mechanism involved is not clear. The results in figure 1 show iproniazid does not block the initial decay of norepinephrine from brain homogenate. This may indicate the processes of catabolism are essentially intact in this tissue despite the presence of iproniazid. Later, however, the decay is markedly slowed to the point where the norepinephrine concentration essentially remains constant after 3 hours of incubation.

The ability of magnesium to counteract the effect of iproniazid on norepinephrine metabolism in rat brain homogenate may be nonspecific. Chaix et al. (8) showed that heavy metal ions (Cu, Ni, Mn) accelerate the oxidation of adrenaline in an in vitro phosphate buffer system. Magnesium, in the concentration employed in this study, may have had an analogous effect on the oxidation of norepinephrine in rat brain homogenate. The action of magnesium in minimizing the increase in activity of mice treated with iproniazid and DOPA may likewise be nonspecific owing to the well-known CNS effect of magnesium.

Oxalate was added to the homogenate systems to inhibit catechol-O-methyltransferase by tying up divalent ions necessary as cofactors for this enzyme. The concentration used corresponds to that employed in preventing blood clotting. The lack of effect in brain homogenate indicates that inhibition of catechol-O-methyltransferase has little influence on the degradation of norepinephrine in brain and is of minimal importance in the metabolism of norepinephrine in this tissue.

The disappearance of norepinephrine from rat heart homogenate differs from that of brain in several ways. The effect of iproniazid becomes significant more quickly in heart than brain, but the plateau effect evident in brain is not seen in heart. Oxalate slowed the disap-

1

ALKYL

- 01 0 ALKANES
1 1C
2 2C
3 3C
4 4C
5 5C
6 6C
7 7C
8 8C
9 9C
10 10C
11 10+C
12 02 12
13 02 0
14 1
15 2
- 0210, 15
3015, 5
1663, 75
3885, 75
0745, 75
3561, 25
2288, 75
2285, 75
3392, 25
3311, 25
1245, 5
0210, 11
0210, 14
0210, 12
0210, 13
- 0210, 15
3015, 5
1663, 75
3885, 75
0745, 75
3561, 25
2288, 75
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0210, 16
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ALKENES

- 3 ALKENES
4 =CH₂
5 C=C
6 3C
7 4C
8 5C
9 6C
10 7C
11 8C
12 9C
13 10C
14 10+C
15 3
16 4
17 5
18 6
- 0211, 2
3015, 75
0022, 5
3906, 5
0747, 5
3565, 5
0211, 3
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- 7 ALKYNES
8 C≡C
9 C≡C
10 3C
11 4C
12 5C
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14 1
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ARYL

- 6 BENZENE
7 MONOSUB
8 DISUB
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- 6 CYCLOALKANES
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8 5M
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CARBONYL

- 1 CARBONYL
2 C=O
3 HO=O
4 C=S
5 HC=S
6 O=(RING)
7 S=(RING)
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1 -COO-ESTER
2 COOH
3 CARBOXY HALIDES
4 F-C=O
5 Cl-C=O
6 Br-C=O
7 I-C=O
8 OCOO
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0805, 75
0805, 5

S-COOR

- 1 S-COOR
2 THIO ACIDS (CXXH)
3 S=C-O
4 O=C-S
5 -S-COOH
6 S=C-HALOGEN
7 S=C-Br
8 S=C-Cl
9 S=C-F
10 S=C-I
11 POLY USAGE
12 MISC.
- 5090, 15
5090, 12
5091, 5
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S-HETERO

- 1 S-HETERO
2 3, 4M
3 5M
4 6M
5 7+M
6 O-CONT.
7 N-CONT.
8 OTHER-CONT.
9 IS
10 2S
11 3+S
12 0
13 1
14 2
15 3
16 4
17 5
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- 4863, 10
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N-HETERO

- 4 N-HETERO
5 3, 4M
6 5M
7 6M
8 7+M
9 O-CONT.
10 N-CONT.
11 OTHER-CONT.
12 0
13 1
14 2
15 3
16 4
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- 3298, 10
3298, 14
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O-HETERO

- 8 O-HETERO
9 3, 4M
10 5M
11 6M
12 7+M
13 0
14 1
15 2
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- 3475, 10
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3475, 21

N, C, S

- 11 N, C, S
12 =N-C=S
13 0
14 0
15 0
16 0
17 0
18 0
19 0
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21 0
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99 0
100 0
- 3297, 5
5090, 16
1598, 75
5091, 7
5091, 20
2618, 5
3297, 7
3297, 6

N, C, O

- 6 N, C, O
7 NC(=O)-N-N
8 -N-C(=O)-O-
9 =N-C(=O)-N-
10 -C(=O)-N-
11 -N-C=O
12 -O-CN
13 0
14 0
15 0
16 0
17 0
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99 0
100 0
- 3297, 2
4462, 5
0785, 25
5361, 5
0785, 75
2613, 25
1222, 5
3297, 4
3297, 3

C, N

- 3 C, N
4 CN
5 -N=C
6 -N-C=N
7 -N-C(=N)-N-
8 -N=C=N-
9 POLY USAGE
10 MISC.
- 0797, 25
1223, 5
2613, 75
0239, 2
2150, 5
0787, 5
0797, 75
0797, 5

OH, SH

- 15 12 OH, SH
16 0
17 0
18 0
19 0
20 0
21 0
22 0
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97 0
98 0
99 0
100 0
- 3298, 6
3298, 4
3298, 25
3298, 8

N, O, (S)

- 3 N, O (S)
4 =N-OH
5 =N-SH
6 -NO₂
7 -N=O
8 -N-N=O
9 N-NO₂
10 POLY USAGE
11 MISC.
- 3298, 27
2391, 2
2968, 75
3295, 5
3299, 75
3299, 25
3299, 5
3299, 29
3299, 27

S, O, (N)

- 8 S, O (N)
9 O=S=O
10 SO₃H
11 S=O
12 SO₂-N
13 POLY USAGE
14 MISC.
- 4863, 25
4860, 75
4860, 25
4859, 5
4860, 5
4863, 27
4863, 26

O, S

- 7 O, S
8 -O-
9 -O-O-
10 -S-
11 -S-S-
12 -S-S-S-
13 0
14 0
15 0
16 0
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100 0
- 3475, 26
3468, 75
3567, 5
5090, 10
1398, 25
5257, 5
3

CHEMISTRY (STIA)

& TECHNOLOGY

403893

74 75 76 77 78 79 80

6/5

6/6/63

S - HETERO

4863.10 1 S-HETERO
4863.14 2 3, 4M
4863.15 3 5M
4863.16 4 6M
4863.17 5 7+M
4863.21 6 O-CONT.
4863.20 7 N-CONT.
4863.22 8 OTHER-CONT.
4863.11 9 IS
4863.12 11 2S
4863.12 10 12 3+S
4863.19 11 0 IND
4863.18 1 FUSED
4863.24 2 SPIRO
4863.23 3 POLY USAGE

N - HETERO

3298.10 4 N-HETERO
3298.14 5 3, 4M
3298.15 6 5M
3298.16 7 6M
3298.17 8 7+M
3298.20 9 O-CONT.
3298.23 11 S-CONT.
3298.21 11 12 OTHER-CONT.
3298.12 12 0 IN
3298.12 1 2N
3298.13 2 3+N
3298.24 3 SALT
3298.19 4 IND
3298.18 5 FUSED
3298.25 6 SPIRO
3298.22 7 POLY USAGE

O-HETERO

3475.10 8 O-HETERO
3475.13 9 3, 4M
3475.14 11 5M
3475.15 12 12 6M
3475.16 13 0 7+M
3475.19 1 N-CONT.
3475.22 2 S-CONT.
3475.20 3 OTHER-CONT.
3475.11 4 I-O
3475.12 5 2+O
3475.18 6 IND
3475.17 7 FUSED
3475.23 8 SPIRO
3475.21 9 POLY USAGE

N, C, S

3297.5 11 N,C,S
5080.16 13 12 =N-C-S
1398.75 14 0 =N-C(=S)-S
5081.7 1 =N-C(=S)-NE
5081.20 2 =S-CN
2618.5 3 =N=C=S
3297.7 4 POLY USAGE
3297.6 5 MISC.

N, C, O

3297.2 6 N,C,O
4462.5 7 NC(=O)-N-N-
0785.25 8 =N-C(=O)-O-
5361.5 9 =N-C(=O)-N-
0785.75 11 =C(=O)-N-
2613.25 14 12 =N-C=O
1222.5 15 0 =O-CN
3297.4 1 POLY USAGE
3297.3 2 MISC.

C, N

0797.25 3 C,N
1223.5 4 CN
2613.75 5 =N=C
0239.2 6 =N-C=N
2150.5 7 =N-C(=N)-N-
0787.5 8 =N=C=N-
0797.75 9 POLY USAGE
0797.5 11 MISC.

OH, SH

3298.27 15 12 OH, SH
2391.2 16 0 OH
2968.75 1 SH
3298.5 2 POLY USAGE

N, O, (S)

3298.27 3 N,O (S)
2391.2 4 =N-OH
2968.75 5 =N-SH
3298.5 6 =NO2
3298.75 7 =N=O
3298.25 8 =N-N=O
3298.5 9 N-NO2
3298.29 11 POLY USAGE
3298.27 16 12 MISC.

S, O, (N)

4863.25 17 0 S, O (N)
4860.75 1 O=S=O
4860.25 2 SO3H
4860.5 3 S=O
4860.5 4 SO2-N
4863.27 5 POLY USAGE
4863.26 6 MISC.

O, S

3475.26 7 O,S
3468.75 8 -O-
3587.5 9 -O-O-
5090.10 11 -S-
1398.25 17 12 -S-S-
5257.5 18 0 -S-S-S-
3475.28 1 POLY USAGE
3475.27 2 MISC.

AMINES

0239.5 3 AMINES
3852.5 4 NH2- (PRI)
4442.5 5 =NH- (SEC)
5036.5 6 =N- (TER)
3984.5 7 =N= (QUAT)
2442.5 8 =N
0503.5 9 =N=N-
1329.5 11 N=N (N=N=)
2359.5 18 12 =N-N-
5251.5 19 0 N=N=N-
0531.5 1 N
N=N
1883.4 2 FLUOROAMINES
1883.8 3 =NF2
1883.6 4 =NF
1884.5 5 F2N-NF-
0239.4 6 SALT (NON-QUAT)
0239.9 7 POLY USAGE
0239.7 8 MISC.

PHOSPHORUS

3634.2 9 PHOSPHORUS RAD.
3634.16 11 P=O,S,O
3634.18 19 12 P=S,2O
3634.17 20 0 P=O, S, 2O
3634.15 1 S=P-O3
3634.15 2 S=P-F
3634.14 3 S=P-F
3634.11 4 O=P(N) (O)-F
3634.10 5 O=P, (F), 2N
3634.13 6 O=P(F) O2
3634.12 7 O=P-F
3634.23 8 P,S-(1 TO 3S)
3634.24 9 P,S-(4S)
1224.75 11 CYCLIC P
3632.25 20 12 P(+3)
3632.75 21 0 P(+5)
3617.5 1 PO4
3634.21 2 P-MISC.
3634.25 3 P,S-MISC.
3634.22 4 POLY USAGE

BORANES

SILANES

MISCELLANEOUS

22 23
0 0
1 1
2 2
3 3
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METALS AND METALLOIDS

2140 24 0 GROUP I
0206 1 ALKALI
0877 2 Co
1925 3 Fe
2787 4 Li
3806 5 K
4592 6 Na
4365 7 Rn
1134 8 Cu
2102 9 Au
4542 11 Ag

2141 24 12 GROUP II
0206 25 0 ALKALINE
0536 1 Ba
0573 2 Be
0760 3 Ca
2845 4 Mg
4110 5 Ra
4821 6 Sn
0755 7 Co
0970 8 Ho
5585 9 Zn

2142 11 GROUP III
0043 25 12 Ac
0232 26 0 Al
1996 1 Ga
2467 2 In
2707 3 La
4410 4 Sc
5055 5 Ti
5583 6 Y

2143 7 GROUP IV
2072 8 Ge
2201 9 Hf
2719 11 Pb
5128 26 12 Sn
5139 27 0 Tl
5590 1 Zn

2144 2 GROUP V
0330 3 Se
0610 4 Br
3287 5 Nb
6 P
4956 7 Ta
5381 8 V

2145 9 GROUP VI
0883 11 CHALCOGENS
3781 27 12 Po
4457 28 0 Se
0935 1 Cr
3122 2 Mo
5277 3 W

2146 4 GROUP VII
5223 5 TRANS. ELEM.
0992 6 Co
2604 7 In
2607 8 Fe
3276 9 Ni
3456 11 Os
3492 29 12 Pd
3744 29 0 Pt
4277 1 Rh
4373 2 Ru

2

pearance of norepinephrine from heart homogenate in three experiments but had no such effect on that from brain. Heart homogenate therefore metabolizes norepinephrine in a manner different from that of brain.

The results of this study are essentially in agreement with those of Goldberg and Shideman (9), who traced the disappearance of added norepinephrine from rat heart homogenate. Both studies show that a monoamine oxidase inhibitor delays the metabolism of norepinephrine in rat heart homogenate. The effect of oxalate noted in this study does not necessarily conflict with the results of Goldberg and Shideman, who concluded that catechol-O-methyltransferase was of little import in the metabolism of norepinephrine in rat heart. The observation that oxalate inhibits the disappearance of norepinephrine from rat heart homogenate may have no relation to the catechol-O-methyltransferase system.

Axelrod et al. (10) have stated that the monoamine oxidase inhibitor, Catron, inhibits the release of norepinephrine from its bound form. Although this is a very plausible explanation of the action of monoamine oxidase inhibitors, especially in the light of this study, the data given by Axelrod et al. to support this hypothesis are not conclusive. They showed that the loss of radioactive norepinephrine from the hearts of Catron-treated rats is slower than that from controls. Axelrod and co-workers, however, failed to consider that norepinephrine taken up by the heart from the circulation may be stored and released in a manner different from that for endogenous material (11). They also apparently did not consider that the Catron-treated hearts differ from controls in endogenous norepinephrine content (7) and that this difference may be responsible for the results obtained.

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| <p>USAF School of Aerospace Medicine, Brooks AF Base, Tex.</p> <p>SAM-TDR-62-138. METABOLISM OF NOREPINEPHRINE IN RAT TISSUE HOMOGENATES. Dec. 62, 5 pp. incl. illus., 11 refs.</p> <p>Unclassified Report</p> <p>In this study, tissue homogenates served as convenient systems in which to investigate the metabolism of norepinephrine. Iproniazid was found to delay the disappearance of norepinephrine from rat brain homogenate. The effect became significant after 4 hours of incubation. High concentrations of magnesium (1.2×10^{-2} M) counteracted this effect of</p> | | | <p>1. Norepinephrine</p> <p>2. Metabolism of norepinephrine</p> <p>I. AFSC Task 775202</p> <p>II. Borowitz, J. L., Merritt, J. H.</p> <p>III. In ASTIA collection</p> | | |
| <p>USAF School of Aerospace Medicine, Brooks AF Base, Tex.</p> <p>SAM-TDR-62-138. METABOLISM OF NOREPINEPHRINE IN RAT TISSUE HOMOGENATES. Dec. 62, 5 pp. incl. illus., 11 refs.</p> <p>Unclassified Report</p> <p>In this study, tissue homogenates served as convenient systems in which to investigate the metabolism of norepinephrine. Iproniazid was found to delay the disappearance of norepinephrine from rat brain homogenate. The effect became significant after 4 hours of incubation. High concentrations of magnesium (1.2×10^{-2} M) counteracted this effect of</p> | | | <p>1. Norepinephrine</p> <p>2. Metabolism of norepinephrine</p> <p>I. AFSC Task 775202</p> <p>II. Borowitz, J. L., Merritt, J. H.</p> <p>III. In ASTIA collection</p> | | |
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iproniazid. Large doses of magnesium, however, did not affect the increased brain norepinephrine level produced by iproniazid in rats. Oxalate, 3.2×10^{-2} M, did not inhibit the decay of norepinephrine in rat brain homogenates, but in one experiment it enhanced the effect of iproniazid in this system. In a limited number of experiments, both iproniazid and oxalate delayed the disappearance of norepinephrine from rat heart homogenate.

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